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2.	Patent application number *(The Patent Office will fill in this part)*	**9915311.6**
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**ISIS INNOVATION LIMITED** **2 SOUTH PARKS ROAD** **OXFORD OX1 3UB** **UNITED KINGDOM**
	Patents ADP number *(if you know it)*	39985 64001
	If the applicant is a corporate body, give the country/state of its incorporation	**UNITED KINGDOM**
4.	Title of the invention	**MODULATION OF DENDRITIC CELL MATURATION**
5.	Name of your agent *(if you have one)*	**BOULT WADE TENNANT**
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**27 FURNIVAL STREET** **LONDON** **EC4A 1PQ**
	Patents ADP number *(if you know it)*	**42001**

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MODULATION OF DENDRITIC CELL MATURATION

The invention relates to the field of immune suppression and, in particular, to the identification of molecules which act as agonists of the cell surface receptors CD36 and/or CD51 as expressed on mammalian dendritic cells and other antigen-presenting cells, to *ex vivo* and *in vivo* uses of such molecules for inducing peripheral immune tolerance in mammals, to identification of molecules which inhibit the state of immune tolerance induced in a human by the binding of red blood cells infected with the malarial parasite to dendritic cells and to *in vivo* uses of such molecules in treating malaria.

Dysfunction of the immune system has been shown to play a role in the initial development and further progression of many human diseases. Impaired immune function can result in inability to fight infection or to destroy malignant cells as they develop within the body. Other diseases are caused because the immune system mounts an inappropriate response to a particular antigen. This inappropriate response might be to an external antigen resulting in atopic disease such as hay fever, asthma, eczema, coeliac disease and the like or to the body's own antigens resulting in auto-immune disease. For example both the non-organ specific auto-immune diseases, such as systemic lupus erythromatosis and rheumatoid arthritis and the organ specific auto-immune diseases such as auto-immune haemolytic anaemia and idiopathic thrombocytopenic purpura are associated with an inappropriate T-cell response to self-antigens.

Other auto-immune diseases where the antigen has been defined include auto-immune connective tissue syndromes, insulin dependent diabetes mellitus and

auto-immune thyroid disease. Diseases where the antigen is less well defined include auto-immune skin diseases such as eczema, psoriasis, alopecia areata and vitiligo, auto-immune diseases of the gastro-intestinal system such as inflammatory bowel disease and auto-immune hepatitis, auto-immune diseases of the nervous system such as multiple sclerosis and myasthenis gravis and auto-immune diseases of the kidney such as glomerulonephritis.

In view of the diseases associated with inappropriate immune response, particularly T-cell response, it is highly desirable to develop pharmaceuticals which are able to damp down certain of the body's immune defence mechanisms in order to alleviate the distressing symptoms associated with these diseases.

As well as treatment of diseases specifically associated with a mal-function of the immune system, down-modulation of immune mechanisms is desirable in recipients of transplants in order to prevent rejection of the transplanted organ or cells. For example an allogeneic response in the case of allogeneic bone marrow transplantation or donor lymphocyte infusion might be avoided if one could induce a state of peripheral immune tolerance against donor cells in the recipient.

A cellular immune response is mediated by T-lymphocytes which are activated by antigen presenting cells, the most important of which are dendritic cells, which present antigen and activate memory T-cells and naive T-cells. Dendritic cells become potent antigen-presenting cells when exposed to an immune stimulus and thereafter are described as "mature". Maturation confers enhanced ability to stimulate T-cells and a reduction in pinocytosis

compared with immature cells. Furthermore, maturation is accompanied by enhanced cell surface expression of HLA Class I and class II molecules as well as adhesion molecules, including CD54 and co-stimulatory molecules such as CD80, CD86 and the cell-surface marker CD83.

Immature dendritic cells present the cell surface antigens CD36 and CD51 (α_v) (part of the vibronectin receptor $\alpha_v\beta_3$). CD36 and CD51 can be cross-linked by the soluble bridging molecule thrombospondin (TSP). Through studies of malarial infection the present inventors have discovered that dendritic cell maturation on exposure to an immune stimulus, for example, lipopolysaccharide (LPS), can be inhibited by molecules which bind to CD36 or to CD51 or both via the bridging molecule TSP and which act as agonists thereto.

This discovery is based on the inventors' observations that red blood cells infected with the material parasite *Plasmodium falciparum* adhere to dendritic cells via CD36 and/or TSP/CD51 (see Figure 1) and are able to inhibit the maturation thereof on exposure to LPS.

Plasmodium falciparum is one of the most successful human pathogens for which virulence factors remain poorly defined, although adhesion of infected erythrocytes to venular endothelium has been associated with some of the symptoms of severe disease. Immune responses are unable to prevent symptomatic infections throughout life and immunity to severe disease develops only slowly during childhood. Understanding the obstacles to the development of protective immunity is crucial for rational approaches to prevent the disease.

Specific immunity to malaria has been attributed to cytotoxic lymphocytes active against the liver

stage of infection or to antibodies reacting against blood stage antigens. Antigenic diversity, clonal antigenic variation and T-cell antagonism may contribute to evasion of the protective and parasiticidal host responses.

Furthermore, it is known that *Plasmodium falciparum*-infected erythrocytes adhere to endothelial cells and it has been widely assumed that this adhesion has evolved to mediate sequestration of parasites to endothelial cells in the peripheral tissues and so reduce their distruction by splenic macrophages.

The present inventors have now identified a further mechanism by which the malarial parasite prevents the infected host from mounting an effective immune response and preventing recurrence of the disease.

Specifically, the inventors have observed that human erythrocytes which are infected with *Plasmodium falciparum* are capable of adhering to human dendritic cells and that immature dendritic cells exposed to infected erythrocytes are no longer able to mature into full antigen-presenting cells or to stimulate T-cell proliferation, when subsequently exposed to an immune stimulus. However, this state of immune tolerance is not observed when the dendritic cells are exposed to uninfected erythrocytes, uninfected erythrocyte lysate, infected erythrocyte lysate, parasite-conditioned medium or a crude pigment preparation derived from infected erythrocytes. Further, the effect is not observed when dendritic cells are exposed to erythrocytes infected with a *Plasmodium falciparum* strain T9/96 which is known not to be able to adhere to endothelial cells (Gardner et al (1996) Proc. Natl. Acad. Sci. USA 93 pp 3503-3508).

This particular strain is not able to induce expression on the surface of infected erythrocytes of the parasite-derived protein pf-EMP-1 which is known to undergo clonal antigenic variation and is thought to be the mediator of adherence to endothelial cells. It has been reported that most parasite lines and clones adhere to the known cell-surface receptors CD36 and via TSP to CD51/61 ($\alpha_v\beta_3$). It is also known that pf-EMP-1 can bind to CD36 and TSP (see WO 96/33736).

The present inventors have now shown that CD36 and CD51 influence the process of dendritic cell maturation and that agonists thereof, including the malarial parasite derived protein pf-EMP-1 and antibodies specific for CD36 and CD51, are able to inhibit dendritic cell maturation in response to an immune stimulus and hence induce a state of immune tolerance. It follows that agonists of CD36 and CD51 would be useful for the treatment of the types of autoimmune disease described above where an over-reaction of the host immune system is responsible for the symptoms. In addition CD36 and CD51 agonists are potentially useful for inducing a state of immune tolerance in both host and donor dendritic cells where bone marrow transplantation or lymphocyte infusion is contemplated. The ability to inhibit maturation of dendritic cells can be demonstrated *in vitro* so that molecules which act as CD36 or CD51 agonists can be easily identified.

Thus, in accordance with a first aspect the invention provides a method of identifying a molecule which is an agonist of cell surface receptor CD36 and/or CD51 as expressed by mammalian dendritic cells which method comprises:

a) exposing immature mammalian dendritic cells to the

molecule to be tested,

b) exposing said immature dendritic cells to an immune stimulus and

c) determining the degree of maturation manifested by said dendritic cells,

wherein impaired maturation in response to the immune stimulus is an indication that said molecule under test is a CD36 and/or CD51 agonist.

Preferably, the method is performed using human dendritic cells. As used herein the term dendritic cells means cells that present antigen to and activate lymphocytes and which are distinguished by their ability to activate, not only memory T-cells but also naive T-cells. Dendritic cells for use in the method of the invention may be derived by cultivation of adherent peripheral blood mononuclear cells with the addition of Granulocyte-Macrophage Stimulating Factor and Interleukin-4 for about 6 to 10 days. Such dendritic cells can be characterised by their level of expression of the cell-surface markers HLA Class I and II (high), CD11 c (high), CD23 and CD19 (negative), CD14 (low) and CD86 (high). These markers distinguish them from B-cells which are positive for CD19, T-cells which are positive for CD3 and macrophages which are CD14 high and CD86 low. (See Banchereau et al, (1998) Nature 392, 245-252). Antibodies to HLA Class I, HLA class II, CD14, CD3, CD19 and CD86 useful for identifying immature dendritic cells are commercially available as indicated in Table 1 below.

Dendritic cells which may be used in the method of the invention can also be derived directly from circulating peripheral blood mononuclear cells or by

culture of CD34+ stem cells.

There are various ways in which maturation of dendritic cells in response to an immune stimulus, may be measured. On maturation the dendritic cells become potent antigen presenting cells. As aforesaid maturation is accompanied by enhanced cell surface expression of HLA Class I and II molecules such as HLA DR, adhesion molecules such as CD54 and co-stimulatory molecules such as CD40, CD80, CD83 and CD86. Thus, examination of the cell's antigen presenting ability, for example variety of antigens and/or level of expression, is one way of determining whether maturation has occurred or whether it has been inhibited by the test molecule. Preferably, following immune stimulation, the level of expression of the HLA Class I and II molecules and/or adhesion molecules and/or co-stimulatory molecules is measured. In one embodiment maturation of dendritic cells is detected by measurement of the level of expression of two or more of the cell-surface antigens HLA DR, CD54, CD40, CD83 and CD86 whose level of expression is particularly enhanced. Preferably, the level of expression of all of the above in response to an immune stimulus is measured. Optionally the expression level of CD80 may also be measured.

Methods by which the expression of a cell-surface antigen may be quantified are well-known to those skilled in the art. The commonly used method is to apply an antibody specific for the antigen in question to the antigen-presenting cells which has been labelled to give a quantifiable detectable signal. Suitable labels are well-known to those skilled in the art and include radioactive labels, enzyme labels, fluorescent labels, metallic particles and the like. Antibodies suitable for carrying out the screening

method of the present invention, as well as a commercial source, are shown in Table 1 below:

TABLE 1

Antigen	Antibody	Source
HLA DR	BF-1	Serotec
HAL Class 1	W32/6	ATCC HB-95
CD14	Tük4	DAKO
CD54	6.5B5	DAKO
CD40	LOB7/6	Serotec
CD80	BB1 or DAL 1	Serotec
CD83	HB15a	Serotec
CD86	BU63	Serotec
CD3	OKT3	ATCC CRL-8001
CD19	HD37	DAKO
CD36	clone 89	Serotec
	clone SMΦ	Immunocontakttec

Serotec: 22 Bankside, Station Approach, Kidlington, Oxford, UK DAKO Ltd: 16 Manor Courtyard, Hughenden Avenue, High Wycombe, Bucks HP13 5RE Immunokontakt: Centro Nord-Sud, CH-6934 Bioggio, Switzerland, Peprotec: 23 St. James Square, London SW9Y 4JH, UK, ATCC: 10801 University Boulevard, Manassas, VA 20110-2209; USA, Sigma: Sigma Alderich Company Ltd: Fancy Road, Poole, Dorset, BH12 4QH, UK, Schering-Plough: Schering-plough House, Shire Park, Welwyn Garden City, Herts, AL7 1TW.

As an alternative to measuring the level of cell surface antigen to determine whether or not dendritic cell maturation has occurred, it is possible to measure the cell's ability to induce T-cell

proliferation. This is inhibited by agonists of CD36 or CD51. Dendritic cells which have been exposed to the molecule to be tested and to an immune stimulus may be exposed to T-cells, for example allogeneic lymphocytes in a mixed lymphocyte reaction (MLR)with the T-cell receptor. The T-cells respond by growing and dividing, something which can easily be measured using methods well-known to one skilled in the art. For example, growth and division can be assessed visually using a light microscope to observe clumps of dividing cells. Alternatively, cell proliferation can be quantified using a suitably labelled metabolite, for example tritiated thymidine, which is incorporated into the cell's DNA.

In the screening method of the invention a variety of immune stimuli may be used. Suitable examples are lipopolysaccharide (available from Sigma), TNFα (available from Peprotec) and monocyte conditioned medium (MCM)the preparation of which is described by Romani et al (1996) J. Immunol. Methods,Sep 27; **196**(2):137-51. Another suitable immune stimulant is CD40L which is expressed from plasmids having the ATCC Accession No's 79812,79813,79814 or 79815. The plasmids may be expressed in mouse fibroblasts STO (ATCC-CRL-1503).

In a particular embodiment of the method of the invention immature dendritic cells (about 10^6) are exposed in duplicate to various concentrations of the test molecule for about 3 to 12 hours in a multiwell plate. The test compound is prepared in a suitable diluent which is not toxic to the dendritic cells such as tissue culture medium, PBS, water or a suitable non-toxic organic solvent, if appropriate. The duplicate wells are subsequently exposed to LPS (about 500 ng/ml) or left untreated for about 48 hours. For

each concentration of the compound and time of exposure, the surface expression of the molecules identified above is compared with the surface expression on immature dendritic cells exposed to the test compound as well as untreated immature dendritic cells. The increase in cell surface expression is evaluated using indirect immunofluorescence and FACScan analysis. A compound is a candidate for further evaluation if the surface expression on dendritic cells of at least two cell-surface antigens is not increased by addition of the immune stimulant, LPS.

Preferably, molecules identified as potential CD36 or CD51 agonists by the method of the invention will be subject to further evaluation. For example, if surface expression of lineage-specific molecules has been used to determine the degree of maturation it would be usual to check whether the compound can also prevent immune-stimulated dendritic cells from inducing proliferation of T-cells and visa versa. In addition direct binding of the candidate molecule to CD36, CD51 or TPS should also be confirmed. This may be easily achieved by applying a sample of the candidate molecule to a purified sample of CD36, CD51 or TPS. 'Purified CD36 may be prepared as described by Tandon et al (1989) The Journal of Biological Chemistry, 264 pp 7570-7575. Purified CD51 may be prepared as described by Smith et al, (1990), Journal of Biological Chemistry, 265, 11008-11013 and purified TSP may be prepared as described by Silverstein et al (1985), Journal of Clinical Investigation, 75, pp 2065-2073.

Tests to detect binding of the test molecule are conveniently carried out by immobilizing the CD36, CD51 or TSP to a solid surface, for example the

surface of a well of a microtitre plate. Methods of immobilization of protein molecules on such surfaces are well-known to those skilled in the art. The test molecule identified as a CD36 or CD51 agonist is then applied to the immobilized protein. Following removal of unbound test molecule the presence of bound molecule is directly detected. This may be achieved in a number of ways depending on the chemical or biochemical characteristics of the test molecule.

For example where the test molecule is a protein it would be usual to detect binding with a labelled antibody to that protein. If the test molecule is a non-antigenic small molecular weight compound then the compound itself may be radioactively labelled for detection.

The molecule whose activity is to be tested in the method of the invention may have any type of molecular structure. For example, it may be a protein, a peptide, an amino acid, DNA, RNA, PNA, a nucleotide or a nucleoside, or a low molecular weight compound. It may be a molecule having known pharmacological or biochemical activity or a molecule with no such known activity and may be a novel molecule. The method of the invention is suitable testing entire libraries of molecules, for example libraries such as would be created by combinatorial chemistry.

Using the method of the invention the present inventors are able to confirm that the *Plasmodium falciparum* derived protein pf-EMP-1 is an agonist of both CD36 and CD51. In particular a fragment of pf-EMP-1 known as CIDR/A4 which comprises the CD36 binding domain is an agonist of CD36. CIDR/A4 is described by Smith et al (1998) Molecular and Biochemical Parasitology, 97, pp 133-148 and comprises

amino acids 402 to 846 of pf-EMP-1 as shown in Figure 2.

Antibodies which bind CD36 and CD51 have also been identified as having agonist activity and are capable of inhibiting the maturation of dendritic cells. Thrombospondin is also an agonist of CD51. The present invention is also directed to any molecule identified as an agonist of CD36 or CD51 by the methods described herein.

In accordance with a second aspect the invention provides a pharmaceutical composition suitable for inducing immune tolerance in a mammal which comprises an agonist of the cell surface receptor CD36 as expressed on mammalian dendritic cells and a pharmacologically acceptable carrier or diluent. The CD36 agonist may be a molecule identified by the method described above. Agonists which are suitable for incorporation into a pharmaceutical composition in accordance with the invention for the treatment of humans include antibodies with an affinity for an epitope of CD36, in particular an antibody which blocks the binding domain on CD36 for pf-EMP-1. Monoclonal antibodies specific for CD36 which are designated "clone 89" and "clone SMΦ " and which are commercially available from Serotech or Immunocontact(details above) are suitable for use in the pharmaceutical compositions of the invention. Other commercially available CD36 antibodies which may be included in pharmaceutical compositions are listed in Appendix 1. It is contemplated that compositions comprising antibodies bispecific against CD36 and CD51 will be useful for inhibiting dendritic cell maturation.

Other agonists suitable for inclusion in pharmaceutical compositions are all variants of the

Plasmodum falciparum pf-EMP-1 or fragments of such proteins which comprise the binding domain for CD36. A particular example is the fragment CIDR/A4 described herein comprising amino acids 402 to 846 of pf-EMP-1. (Figure 2).

Pharmaceutical compositions comprising a bispecific CD36 antibody and the CIDR/A4 fragment are also contemplated in accordance with the invention.

In a third of its aspects the invention provides a pharmaceutical composition suitable for inducing peripheral immune tolerance in a mammal which comprises an agonist of the cell surface receptor CD51 as expressed by mammalian dendritic cells and a pharmacologically acceptable carrier or diluent. As with CD36 acceptable agonists are antibodies, preferably monoclonal antibodies, directed against an epitope of CD51. Particularly suitable are antibodies blocking the binding domain of CD51 for the bridging molecule TSP. Antibodies suitable for incorporation in a pharmaceutical composition in accordance with this aspect of the invention are commercially available and set out in Appendix 2.

Thrombospondin (TSP) is also suitable for incorporation into a pharmaceutical composition as a CD51 agonist. Preferably, such compositions also include the *Plasmodum falciparum* protein pf-EMP-1 or a fragment thereof incorporating the thrombospondin binding domain of pf-EMP-1.

Pharmaceutical compositions in accordance with the second and third aspects of the invention are useful for the treatment of autoimmune diseases associated with inappropriate dendritic cell maturation and T-cell proliferation such as systemic lupus erythromatosis, rheumatiod arthritis, autoimmune haemolytic anaemia or idiopathic thrombocytopenic

purpura. Liposomes are a suitable vehicle for delivery of CD36 or CD51 agonists *in vivo* but other vehicles suitable for delivery of proteins *in vivo* are well-known to those skilled in the art.

In accordance with a fourth aspect of the invention there is provided a method of treating mammalian dendritic cells *in vitro* to induce immune tolerance therein which comprises exposing said cells to an agonist of cell surface receptors CD36 and/or CD51 as expressed on mammalian dendritic cells. The invention also relates to preparations of cells so treated. Suitable agonists are any of those agonist molecules described above or any molecule identified by the screening method described herein.

Treatment of dendritic cells *ex-vivo* with an agonist of CD36 and/or CD51 is beneficial in the case of bone marrow transplantation or lymphocyte infusion. Recipient cells removed from the body are treated with agonists as described above to induce a state of immune tolerance therein. The treated cells are then re-introduced to the body before or simultaneously with the donor cells and the risk of allogeneic reaction is thereby reduced or eliminated. It is contemplated that dendritic cells of the donor may also be treated with a CD36 and/or CD51 agonist to induce immune tolerance.

It follows from the inventor's observations concerning inhibition of maturation of dendritic cells with agonists of CD36 or CD51 that a similar effect will be observed with other antigen-presenting cells of the immune system which also express CD36 and CD51 such as macrophages, B-lymphocytes and monocytes. Thus, in accordance with a fifth aspect the invention provides a method of identifying a molecule which is an agonist of cell surface receptors CD36 and/or CD51

as expressed on antigen-presenting cells of the mammalian immune system which method comprises:

a) exposing immature mammalian antigen-presenting cells to the molecule to be tested,

b) exposing said immature cells to an immune stimulus and

c) determining the response to said immune stimulus by said cells,

wherein an impaired response compared to the response in the absence of said test molecule is an indication that said molecule under test is a CD36 and/or CD51 agonist.

Preferably, the response that is measured is maturation of said antigen presenting cell. Such a screening method may be carried out in any of the ways already described herein for dendritic cells.

It further follows from the inventors' observation that *Plasmodium falciparum* infected erythrocytes adhere to dendritic cells and inhibit the maturation thereof that molecules which block or inhibit such adherence may be useful as pharmaceuticals in the clinical management of malaria, in particular molecules which inhibit adherence of parasite-infected erythrocytes to CD36 or TSP.

Thus, in accordance with a sixth aspect of the invention a method comprising the following steps is used to identify a molecule capable of preventing adherence of erythrocytes infected with a malarial parasite to human dendritic cells:

(a) exposing a purified preparation of CD36 or TSP to:-

(i) the molecule to be tested and
(ii) parasitsed human erythrocytes

either consecutively or simultaneously and

(b) determining the level of adherence of said parasitised erythrocytes to said CD36 or TSP

wherein a reduction in the level of adherence to CD36 or TSP in the presence of the test molecule compared to the level of adherence in the absence of said test molecule is an indication that said molecule is capable of preventing the adherence of erythrocytes infected with the malarial parasite to human dendritic cells.

The erythrocytes may be infected with *Plasmodium falciparum* or another Plasmodium species. Suitable *falciparum* strains include ITO/A4 or ITO/C24 which may be derived as described by Roberts et al (1992) Nature 357 pp 689-692 or Malayan Camp (MC) which may be obtained as described herein.

A suitable format for carrying out a screening method as described above is to immobilize the purified CD36 or TSP onto a solid surface. Preferably, immobilization is secured by adsorption of the protein molecules to a plastic surface such as a petri dish. Parasitised erythrocytes suspended in a suitable binding medium are added to the adsorbed CD36 or TSP and incubated for a period sufficient to allow adherence, for example, about 1 hour. Thereafter the binding medium and any non-adhered erythrocytes are removed and a suitable erythrocyte stain for example, Giemsa, added to the petri dish. Adhered erythrocytes may be quantified by counting under a light microscope. Alternatively, depending on the stain

used, erythrocyte adherence may be quantified by spectrometry, fluorescence microcopy and the like.

In a seventh aspect the invention provides a method of identifying a molecule capable of preventing the adherence of red blood cells infected with a malarial parasite to human dendritic cells which comprises:

a) exposing immature human dendritic cells to the *Plasmodium falciparum* protein pf-EMP-1 or an active binding domain thereof in the presence or absence of the molecule to be tested,

b) exposing said immature dendritic cells to an immune stimulus and

c) determining the degree of maturation manifested by said dendritic cells,

wherein any maturation of said dendritic cells in the presence of the test molecule over and above that manifested in the absence of said molecule is an indication that said molecule is capable of preventing adherence of red blood cells infected with a malarial parasite to human dendritic cells.

Maturation of dendritic cells may be measured by any of the methods already described herein. Suitable immune stimulants include LPS, TNFα, CD40L and monocyte conditioned medium (MCM). Preferably the pf-EMP-1 preparation for use in the method is that designated in pf-EMP-1 A4var as described by Smith et al (see before) and having the Genbank Accession No. L42244. The fragment CIDR/A4 may also be used.

In a further aspect the invention provides for

use of molecules identified by the aforementioned methods which inhibit infected erythrocyte adherence to dendritic cells in pharmaceutical compositions for the treatment of malarial infection.

Based on the present inventors' observations it is further contemplated that a modified CIDR region of the pf-EMP-1 A4 variant protein could be incorporated in a multisubunit vaccine against *falciparum* malaria. This would induce blocking antibodies against the CD36 binding domain of pf-EMP-1 variant proteins so that the immune responses against other proteins are not inhibited.

Herein reference is made to the following figures:

FIGURE 1 shows schematically the molecular basis for the binding of Plasmodium falciparum infected red blood cells to CD36 and TSP on the surface of dendritic cells;

FIGURE 2 shows the amino acid sequence of the pf-EMP-1 fragment CIDR/A4;

FIGURE 3 shows the expression of dendritic cell marker antigens HLA DR, CD54, CD40, CD80, CD83 and CD86 following immune stimulation after exposure to (a) LPS matured dendritic cells, (b) dendritic cells matured with LPS, with and without prior exposure to RBC, (c) dendritic cells matured with LPS with and without prior exposure to parasite lysate and (d) dendritic cells matured with LPS with and without prior exposure to intact ITO/A4 infected RBC;

FIGURE 4; (A) shows the absolute binding of erythrocytes infected with parasite lines ITO/A4,

ITO/C24, MC and T9/96 to CD54, CD56, and TSP (a,c,e,g) and (B) shows the increase in surface expression of LPS matured dendritic cells compared with dendritic cells exposed to the respective parasite line prior to maturation (b,d,f,h);

FIGURE 5 shows transmission electron micrographs illustrating the interaction of dendritic cells with (a) ITO/A4 infected erythrocytes and (d) non-adherent T9/96 infected erythrocytes;

FIGURE 6 shows dendritic cell stimulation of T-cell proliferation (a) induced by immature dendritic cells (■), LPS-matured dendritic cells (□) and dendritic cells co-cultivated with intact ITO/A4 infected erythrocytes (▼) prior to maturation, primary CD4+ T-cell responses to parasite lysate (b) and to keyhole limpit haemocyanin (c) induced by LPS-matured autologous dendritic cells (□,○) and autologous dendritic cells co-cultivated with intact ITO/A4 infected erythrocytes (■,●)prior to maturation;

FIGURE 7 shows the effect of monoclonal antibodies against CD36 and CD51 on maturation of dendritic cells;

FIGURE 8 shows the effect of apoptotic neutrophils on the maturation of dendritic cells;

EXAMPLE 1

Generation of dendritic cells.

Immature dendritic cells were derived from peripheral human blood cells using standard procedures as

described by Sallusto et al (1995) J. Exp. Med. **182** pp 389-400. Briefly, monocytes were cultivated in RPMI 1640 supplemented with 2mM Glutamine,50 μg/ml Kanamycin, 1% nonessential amino acids (GibcoBRL), 10% human AB serum and 50 ng/ml of each IL-4 (specific activity >$2x10^6$ U/mg, PeproTech) and GM-CSF (specific activity > $1x10^7$ U/mg, Schering-Plough) for 6 days. Between day six and day nine of the culture non-adherent immature dendritic cells were harvested and purified by depletion of contaminating lymphocytes with the aid of magnetic beads (Dynal) and anti-CD3 and anti-CD19 monoclonal antibodies (DAKO).

EXAMPLE 2

Maturation assay.

For maturation assays $1x10^6$ purified dendritic cells were incubated in duplicate wells (a) with 100 ng/ml LPS,(b) with 100ng/ml LPS with or without prior exposure to $1x10^8$ RBC, (c) with 100 ng/ml LPS with or without prior exposure to parasite lysate corresponding to $1x10^8$ parasite infected RBC,(d) 100 ng/ml LPS with or without prior exposure to $1x10^8$ intact ITO/A4 infected RBCs. Incubation with LPS (Salmonella typhimurium) was for a period of 48 hours.

Maturation of the dendritic cells was measured using monoclonal antibodies to the following human cell surface markers: CD3 clone OKT3, HLA A,B,C clone W32/6, CD14 clone Tuk4, CD54 clone 6.5B5, CD19 clone HD37 (DAKO): CD36 clone 89, CD80 clone BB1, CD40 clone LOB7/6, CD86 clone BU63, HLA DR clone BF-1 (Serotec), CD83 clone HB15a (Zhou et al (1995) J. Imm. **154**, pp3821-3835. Staining of dendritic cells was

performed as described by Zhou et al above and immunofluorescence analysed by FACScan (Becton Dickenson). All experiments were repeated at least six times with dendritic cells obtained from different donors. The results are shown on Figure 3. The relative increase of surface expression is expressed as the mean fluorescence intensity (MFI) of matured dendritic cells over the MFI on immature dendritic cells.

The results show that dendritic cell maturation is inhibited by the direct interaction with intact infected erythrocytes and is not due to the secretion of inhibitory parasite products or a toxic effect of parasite debris.

The differences in surface expression on dendritic cells exposed to intact infected erythrocytes to dendritic cells alone are statistically significant for all markers with $p<0.01$ (Student t-test).

EXAMPLE 3

Cultivation of Plasmodium falciparum infected red blood cells.

Laboratory strains of Plasmodium falciparum were cultured in human RBC as described by Trager et al (1976) Science. **193** pp673 to 675. The cytoadherent cell lines ITO/A4 and ITO/C24 were clones isolated by manipulation from the ITO4 line, which is derived from a parasite isolate from Ituxi in Brazil. The cytoadherent parasite line Malayan Camp (MC) and the non-adherent cell line T9/96 were both adapted to in vitro culture from parasites originally isolated from

Thailand. All cultures were free from mycoplasma contamination. Infected erythrocytes were purified either by differential sedimentation in Plasmagel or through 65% Percoll both of which gave a yield of more than 90% infected erythrocytes. Examination of a thin film revealed that more than 90% of infected erythrocyes were viable. Parasite lysate was obtained by three rounds of freezing and thawing of mature infected RBC. Parasite pigment was prepared as described by Schwarzer et al (1994) BR. J. Haematol. **88**, pp740-745. Parasite conditioned medium was the supernatant derived after culturing $1x10^8$ purified infected erythrocytes in dendritic cell medium for 24 hours. All materials were from Sigma unless otherwise stated.

EXAMPLE 4

Binding of parasites to purified proteins.

Binding of parasitised RBCs to purified proteins was measured as previously described by Craig et al (1997) Infect. Immun. **65**, pp 4580-4585. Briefly, two microlitres of a solution of TSP (Gibco-BRL), purified CD36 or purified CD54 (ICAM-Fc) were adsorbed onto bacteriological, plastic plates. Mature erythrocytes parasitised with P. falciparum strains (a) ITO/A4, (c) ITO/C24, (e) MC and (g) T9/96, were suspended in binding medium and added to each dish. The erythrocytes were allowed to settle and then resuspended by gentle rotation every 10 minutes for 1 hour. Non-adherent cells were removed, the remaining cells fixed and stained with Giemsa. Adherent parasitised cells were counted by light microscopy and the number of cells bound per square millimeter were

corrected to binding at 2% haematocrit and 5% parasitaemia. The results are shown in Figure 4A and confirm that like ITO/A4, ITO/C24 and MC are able to adhere to CD36 and TSP. However, their adherence to CD54 was much reduced. T6/96 does not adhere to CD54, CD36 or TSP.

EXAMPLE 5

Effect of parasite strains on maturation.

A maturation assay as described in Example 2 was carried out but exposing immature dendritic cells to erythrocytes infected with (b) ITO/A4, (d) ITO/C24, (f) MC and (h) T9/96. The results are shown in Figure 4B. While parasite lines MC and ITO/C24 inhibited the maturation of dendritic cells in a similar vein to clone ITO/A4, the non-adherent line T9/96 did not inhibit maturation of dendritic cells even at a ratio of infected erythrocytes to dendritic cells of 100:1.

EXAMPLE 6

Electron microscopy

Adherence of ITO/A4 infected erythrocytes but not T9/96 infected erythrocytes to dendritic cells was confirmed by electron microscopy. One million purified immature dendritic cells were incubated for 2 hours and for 12 hours with $1x10^8$ ITO/A4 infected RBC (a) or T9/96 infected (d) in 2 ml of dendritic cell medium , harvested and fixed with 2.5% glutaraldehyde/cacodylate buffer. Cells were post fixed in osmium tetroxide, dehydrated and embedded in epoxy resin. Thin sections were stained with uranyl

acetate and lead citrate prior to examination in a Joel 1200EX electron microscope. The number of adherent and infected erythrocytes and the number of phagosomes containing pigment granules was counted in each sample in thin sections of 100 randomly selected dendritic cells. Transmission electron micrographs are shown in Figure 5.

Note the cell processes partially enclosing infected erythrocytes (arrows in a) and the close apposition of the limiting membranes of the infected erythrocytes and dendritic cells particularly at the knobs (b, arrowhead). Within dendritic cell cytoplasm are phagosomes containing characteristic pigment granules (c, arrows). N -dendritic cell nucleus, P - infected erythrocyte. Bars are 2 μm (a and d), 200 μm (b), 500 μm (c).

ITO/A4 infected erythrocytes were observed to be in intimate contact with immature dendritic cells with cytoplasmic processes partially enclosing the parasites (Fig. 5a). The plasmalemma of the infected erythrocytes was in close apposition to the limiting membrane of the dendritic cell particularly at the site of knobs (Fig. 5b). A similar apposition between parasitised erythrocytes and host cells is seen between infected red blood cells and endothelial cells (Berendt et al (1994) Parasitology 108 Suppl. 519-28). In contrast, only a few infected erythrocytes of the T9/96 strain were associated with the dendritic cells (Fig. 5d). When quantified, ten times more ITO/A4 infected erythrocytes were found adherent to dendritic cells than T9/96 infected erythrocytes in 100 thin sections of dendritic cells. Furthermore, ingestion of intact ITO/A4 infected erythrocytes by dendritic cells

was not observed during this time. Nevertheless, phagocytosis of parasite debris as revealed by the number of phagosomes containing pigment granules (Fig. 5c) was similar for dendritic cells incubated with ITO/A4 or with T9/96.

Example 7

T-cell proliferation assays.

Total-T-cells (allogeneic MLR) or CD4+ T cells (primary T-cell responses) were purified using a Cellect column (TCS). For the allogeneic MLR, dendritic cells were added in increasing numbers (156 to 10,000) to 1 x 10^5 T-cells in triplicate and incubated for 5 days. T-cells were pulsed with 0.5 μCi 3H-thymidine/well for the last 18 hours of the culture. For primary T-cell responses, 1 x 10^6 dendritic cells were incubated with medium alone or with 1 x 10^8 infected erythrocytes for 18 h and then pulsed with 10 μg/ml parasite-lysate or with 30 μg/ml keyhole limpet haemocyanin, respectively. The dendritic cells were purified by sedimentation through Lymphoprep™ and 1 X 10^5 dendritic cells were culterd with 1.5 x 10^6 CD4+ T-cells from the same donor. From day 4 to day 6 of culture, 50 μl aliquots were taken in triplicate and pulsed with 0.5 μCi ^{3}H-thymidine/well for 8 hours.
(see Plebanski et al (1992) Immunol. 75 86-90). The results are shown in Figure 6.

Dendritic cells exposed to intact infected erythrocytes are poor stimulators of T-cell proliferation. Allogeneic T-cell proliferation (a) induced by immature dendritic cells (■), LPS-matured

dendritic cells (□) and dendritic cells co-cultivated with intact ITO/A4 infected erythrocytes (▼) prior to maturation. Primary CD4+ T-cell responses to parasite-lysate (b) and to keyhole limpet haemocyanin (c) induced by LPS-matured autologous dendritic cells (□,○) and autologous dendritic cells co-cultivated with intact ITO/A4 infected erythrocytes (■,●) prior to maturation. Data from one out of three independent experiments are shown.

Dendritic cells matured after incubation with uninfected RBC, a crude pigment preparation or a lysate of infected erythrocytes induced a similar degree of T-cell proliferation in a mixed leukocyte, reaction to that induced by control mature dendritic cells (data not shown).

However, dendritic cells incubated with LPS after exposure to intact infected erythrocytes from the parasite line ITO/A4 were strikingly less efficient in their induction of T-cell proliferation compared with the T-cell proliferation induced by mature dendritic cells (Fig 6a). Furthermore, dendritic cells exposed to intact infected erythrocytes before maturation with LPS did not induce primary CD4+ T-cell responses to lysate of infected erythrocytes or to keyhole limpet haemocyanin (Plebanski et al) (Fig 6, b,c).

It is concluded that the maturation of dendritic cells and their subsequent ability to activate T-cells is profoundly inhibited by their interaction with intact infected erythrocytes. Non-adherent parasite lines, parasite debris and crude pigment do not modulate dendritic cell function in this way. These studies provide one explanation for the

clinical and experimental evidence of immune dysregulation during malaria infection such as the impairment of the delayed-type hypersensitivity response to recall antigens and the antibody response to vaccines.

Example 8

Maturation assay with monoclonal antibody

A maturation assay was carried out as described in Example 2 except that instead of infected erythrocytes the immature dendritic cells were exposed to monoclonal antibodies to CD36, CD51 or both prior to immune stimulation with LPS. The results are shown in Figure 7. As will be apparent both CD36 and CD51 antibodies have the effect of inhibiting dendritic cell maturation in a similar manner to infected erythrocytes.

Example 9

Maturation assay with apoptotic neutrophils.

A maturation assay was carried out as described in Example 2 except that instead of infected erythrocytes the immature dendritic cells were exposed to apoptotic neutrophils prior to immune stimulation with LPS. The results are shown in Figure 8. Apoptotic neutrophils have a similar inhibitory effect on maturation of dendritic cells.

APPENDIX 1

DI is distributor

SD is standard designation

Other MABs are

OKM5 Ortho Pharmaceutical Corporation
OKM8 1001 US Highway 202
P. O. Box 250
Raritan, N.J.

Your query was:
cd36

The selected databases contain 18 documents matching your query:

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2: 1003558 RE 1.CE>platelet 1.U>cell membrane 1.SN>CD36
3: 1018253 RE 1.SN>CD36 1.a.CC>differentiation 1.b.CC>gl
4: 1020319 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
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6: 1020540 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
7: 1017636 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
8: 1022016 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
9: 1019865 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
10: 1024459 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36 1.MW
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12: 1009963 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet
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DI 2382 Camino Vida Roble, Suite I
DI Carlsbad, CA 92009 USA
DI 1-619-438-1886
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DE P>MON1118 ;distributor
PD ;IgG1
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AP ;frozen section

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DI 105 York Street
DI Kennebunkport, ME 04043 USA
DT 1-207-985-1944
DE P>N42540M ;distributor
PD ;IgG1
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RE 1.a.CC>differentiation 1.b.CC>protein
RE 1.c.CC>blood coagulation factor
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DI P>BioGenex Laboratories
DI 4600 Norris Canyon Road
DI San Ramon, CA 94583 USA
DI 1-510-275-0550
DI 1-800-421-4149 (toll free USA)
DE P>1E8 ;distributor
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DI P>Harlan Bioproducts for Science, Inc.
DI P.O. Box 29176
DI Indianapolis, IN 46229-0176
DI 1-317-894-7536
DI 1-800-9-SCIENCE
DE C>89 ;distributor
DE P>MCA1214 ;distributor
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PD ;IgG2b
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DI 1849 Bayshore Blvd. #200
DI Burlingame, CA 94010
DI 1-650-652-0468
DI 1-800-874-4007
DI 2.P>Medica
DI 2382 Camino Vida Roble, Suite I
DI Carlsbad, CA 92009 USA
DI 1-619-438-1886
DE C>VM58 ;developer
DE P>MON1143 ;distributor
DE P>VM58 ;distributor
DE 2.P>MON1143 ;distributor
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Your query was:
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DI Indianapolis, IN 46229-0176
DI 1-317-894-7536
DI 1-800-9-SCIENCE
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DE P>MCA1214 ;distributor
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DI P>Novocastra Laboratories Ltd.
DI 24 Claremont Place
DI Newcastle upon Tyne NE2 4AA, UK
DI 44-0191 222 8550
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DE P>SMO ;distributor
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DI P>O.E.M. Concepts, Inc.
DI 1889 Route 9, Bldg. 25, Unit 96
DI Toms River, NJ 08755 USA
DI 1-732-341-3570
DE C>289-10930 ;distributor
DE P>M2-L69 ;distributor
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DI 199 Saranac Avenue
DI Lake Placid, NY 12946 USA
DI 1-617-890-8845
DI 1-800-233-3991 (toll free USA) (sales)
DE P>05-287 ;distributor
DO G>Mus musculus CN>mouse S>BALB/c O>spleen
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DI P.O. Box 29176
DI Indianapolis, IN 46229-0176
DI 1-317-894-7536
DI 1-800-9-SCIENCE
DI 2.P>Immunotech S.A.
DI Departement commercial
DI Luminy Case 915
DI 13288 Marseille Cedex 9, France
DI 33-91-41-41-38
DI 430246 F IMMTECH
DE C>Fa6-152 ;developer
DE P>MCA 682 ;distributor
DE 2.P>0765 ;distributor
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SO Exp Cell Res 1992;198:85-92
SO J Exp Med 1990;171:1883-92
DI P>Lab Vision-NecMarkers
DI 47770 Westinghouse Drive
DI Fremont, CA 94539 USA
DI 1-800-828-1628
DE C>1A7 ;distributor
DE P>MS-466-P ;distributor
IM G>Homo sapiens CN>human CE>platelet SN>CD36 a.CC>differentiation
IM b.CC>glycoprotein c.CC>receptor
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AB platelet GPIIIb, platelet glycoprotein IIIb, and OKM5-antigen.
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AN 22825
AU Kemshead J
AD Imperial Cancer Research Technology;
AD Sardinia House;
AD Sardinia Street;
AD London WC2A 3NL;
AD UK;
AD TEL 01 242 1136;
AD TELEX 265107 ICFRG;
AD FAX 01 831 4991
SO Br J Haematol 1984;57:621
DE P>M148 ;developer
IM G>Homo sapiens CN>human PA>medulloblastoma a.CC>neoplasm
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RE 4.a.CC>neoplasm
AP ;immunofluorescence ;immunoprecipitation
AB in vivo imaging and therapy
SD M148
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AN 1012380
DI P>Biodesign International
DI 105 York Street
DI Kennebunkport, ME 04043 USA
DI 1-207-985-1944
DI 2.P>Harlan Bioproducts for Science, Inc.
DI P.O. Box 29176
DI Indianapolis, IN 46229-0176
DI 1-317-894-7536
DI 1-800-9-SCIENCE
DI 3.P>Lampire Biological Laboratories
DI P.O. Box 270
DI Pipersville, PA 18947 USA
DI 1-215-795-2838
DI 4.P>Sigma Chemical Company
DI P.O. Box 14508
DI St. Louis, MO 63178 9916 USA
DI 1-800-325-3010 (toll free USA)
DI 1-314-771-5750
DE C>SMO ;developer
DE P>P54168M ;distributor
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DI 105 York Street
DI Kennebunkport, ME 04043 USA
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DI 2.P>Cymbus Bioscience Limited
DI 2 Venture Road
DI Chilworth Research Center
DI Southampton, Hampshire SO1 7NS UK
DI 44-703-767178
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Your query was:
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DI 7 New Fields
DI Stinsford Road
DI Poole BH17 7NF, England
DI UK
DI 44-1202 660006
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DE P>2125-3607 ;distributor
DO G>Mus musculus CN>mouse
PD ;Ig
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
RE 1.a.CC>differentiation
AP ;immunofluorescence
AV ;fluorescein conjugate
AB CD36 is also known as platelet GPIV, GP1V, platelet GPIIIb, GPIIIb, platele
AB glycoprotein IV, and FAT (rat).
SD 21253607
SD SMPHIIGM
LD USA MCM
EI DA>9811
CI ;catalog
SN Synonym>CD36   1024459 SN Synonym>CD36
```

This page was generated by SFgate 5.111.

1016854 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet

```
1016854 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet

AN 1016854
DI P>PharMingen
DI 10975 Torreyana Road
DI San Diego, CA 92121 USA
DI 1-619-677-7737
DI 1-800-848-6227 (toll free USA)
DE P>CB38 ;distributor
DO G>Mus musculus CN>mouse S>BALB/c
PD ;IgM ;kappa
RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet
RE 1.U>cell membrane 1.SN>CD36 1.MW>88 kD
RE 1.a.CC>differentiation 1.b.CC>glycoprotein
AP ;flow cytometry ;immunoprecipitation
AV ;fluorescein conjugate ;purified
SD CB38
LD USA JMJ
EI DA>9504
CI ;catalog
SN Synonym>CD36   1016854 SN Synonym>CD36
```

1012440 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

1012440 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

AN 1012440
DI P>BioSource International
DI 820 Flynn Roa
DI Camarillo, CA 93012 USA
DI 1-800-242-0607(toll free USA)
DI 1-805-987-0086
DI 2.P>Cymbus Bioscience Limited
DI 2 Venture Road
DI Chilworth Research Center
DI Southampton, Hampshire SO1 7NS UK
DI 44-703-767178
DI 3.P>Roche Molecular Biochemicals
DI formerly Boehringer Mannheim GmbH
DI Sandhofer Strasse 116
DI D-68305 Mannheim Germany
DI 49-621-759 8577
DE C>SMO ;developer
DE P>AHS3601 ;distributor
DE P>AHS3608 ;distributor
DE P>CS-CD36-FI ;discontinued designation
DE P>CS-CD36-UN ;discontinued designation
DE P>SMO ;distributor
DE 2.P>CBL 168 ;distributor
DE 2.P>SMO ;distributor
DE 3.P>1441 230 ;discontinued designation
DE 3.P>1441 264 ;distributor
DE 3.P>SMO ;distributor
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
RE 1.a.CC>differentiation
AV ;fluorescein conjugate ;3.purified
SD 1441230
SD 1441264
SD AHS3601
SD AHS3608
SD CBL168
SD CSCD36FI
SD CSCD36UN
SD SMO
LD USA BAL
EI DA>9709 CV>9111
CI ;catalog
SN Synonym>CD36 1012440 SN Synonym>CD36

Your query was:
cd36

1003358 RE 1.SN>ACTH 1.FS>N-terminal region 1.a.CC>ho

```
1003358 RE 1.SN>ACTH 1.FS>N-terminal region 1.a.CC>hormone

AN 1003358
DI P>Biodesign International
DI 105 York Street
DI Kennebunkport, ME 04043 USA
DI 1-207-985-1944
DI 2.P>Cymbus Bioscience Limited
DI 2 Venture Road
DI Chilworth Research Center
DI Southampton, Hampshire SO1 7NS UK
DI 44-703-767178
DE C>58 ;developer
DE P>E54008M ;distributor
RE 1.SN>ACTH 1.FS>N-terminal region 1.a.CC>hormone
AV ;purified
AB CD36 is also known as GPIIIb, GPIV
SD 58
SD E54008M
LD USA BAL
EI DA>9002 CV>9007
CI ;catalog
SN Synonym>ACTH
```

Your query was:
cd36

1019119 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36 1.MW

1019119 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36 1.MW>88 kD

AN 1019119
SO J Cell Biol 1994;269:6011
SO J Cell Biol 1993;268:16179
DI P>Transduction Laboratories
DI 133 Venture Ct., Suite 5
DI Lexington, Ky 40511-9923
DI 1-606-259-1550
DI 1-800-227-4063
DE P>73 ;distributor
DE P>C23620 ;distributor
IM G>Homo sapiens CN>human SN>CD36 FS>amino acids 70-242
IM a.CC>protein
DO G>Mus musculus CN>mouse
PD ;IgG2a
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36 1.MW>88 kD
RE 1.a.CC>protein
RE 2.G>Rattus norvegicus 2.CN>Norway rat 2.SN>CD36
RE 2.MW>88 kD 2.a.CC>protein
RE 3.G>Gallus gallus 3.CN>chicken 3.SN>CD36 3.MW>88 kD
RE 3.a.CC>protein
AP ;Western blot ;immunofluorescence
AV ;purified
SD 73
SD C23620
LD USA JMJ
EI DA>9901
CI ;catalog
SN Synonym>CD36 1019119 SN Synonym>CD36

APPENDIX 2

DI is distributor
SD is standard designation

Your query was:
cd51

1022961 RE 1.SN>CD51 1.a.CC>differentiation

```
1022961 RE 1.SN>CD51 1.a.CC>differentiation

AN 1022961
DI P>Caltag Laboratories
DI 1849 Bayshore Blvd. #200
DI Burlingame, CA 94010
DI 1-650-652-0468
DI 1-800-874-4007
DE C>NGX-IV/110 ;distributor
DE P>MON1027 ;distributor
RE 1.SN>CD51 1.a.CC>differentiation

SD NGXIV110
LD USA MCM
EI DA>9805
CI ;catalog
```

This page was generated by SFgate 5.111.

Your query was:
cd51

1022017 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51/61 c

```
1022017 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51/61 complex

AN 1022017
DI P>O.E.M. Concepts, Inc.
DI 1889 Route 9, Bldg. 25, Unit 96
DI Toms River, NJ 08755 USA
DI 1-732-341-3570
DE C>289-12336 ;distributor
DE P>M2-L69 ;distributor
DO G>Mus musculus CN>mouse
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51/61 complex
RE 1.a.CC>differentiation
AP ;cell surface marker
AV ;purified
AB Reactant#1: CD51/61 complex is also known as integrin alpha V beta 3.
SD 28912336
SD M2L69
LD USA EJK
EI DA>9712
CI ;catalog
SN Synonym>CD51/61 complex   1022018 ****HB/HYBRID
```

Your query was:
cd51

1013413 RE 1.CE>platelet 1.SN>CD51 1.a.CC>differentia

```
1013413 RE 1.CE>platelet 1.SN>CD51 1.a.CC>differentiation

AN 1013413
DI P>Medica
DI 2382 Camino Vida Roble, Suite I
DI Carlsbad, CA 92009 USA
DI 1-619-438-1886
DE C>706 ;developer
DE P>MON1130 ;distributor
PD ;IgG1
RE 1.CE>platelet 1.SN>CD51 1.a.CC>differentiation

SD MON1130
LD USA BAL
ET DA>9303
CI ;catalog
```

Your query was:
cd51

1024461 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

```
1024461 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

AN 1024461
DI P>Biogenesis Ltd.
DI 7 New Fields
DI Stinsford Road
DI Poole BH17 7NF, England
DI UK
DI 44-1202 660006
DE C>13C2 ;distributor
DE P>2125-5108 ;distributor
DE P>2125-5114 ;distributor
DE P>2125-5119 ;distributor
DO G>Mus musculus CN>mouse
PD ;Ig
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51
RE 1.a.CC>differentiation
AP ;immunofluorescence
AV ;R-phycoerythrin conjugate ;fluorescein conjugate
AB CD51 is also known as integrin alpha V subunit and vitronectin receptor
AB alpha subunit.
SD 13C2
SD 21255108
SD 21255114
SD 21255119
LD USA MCM
EI DA>9811
CI ;catalog
```

This page was generated by SFgate 5.111.

Your query was:
cd51

1017037 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

```
1017037 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

DI P>Zymed Laboratories Inc.
DI 458 Carlton Court
DI South San Francisco, CA 94080 USA
DI 1-800-874-4494 (toll free USA)
DI 1-415-871-4494
DE P>07-5103 ;distributor
DE P>NK1-M9 ;distributor
DO G>Mus musculus CN>mouse S>BALB/c
PD ;IgG1
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51
RE 1.a.CC>differentiation 1.b.CC>protein
AP ;flow cytometry ;immunofluorescence
AV ;purified
SD 075103
SD NK1M9
LD USA JMJ
EI DA>9708
CI ;catalog
```

This page was generated by SFgate 5.111.

Your query was:
cd51

1009962 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

```
1009962 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

AN 1009962
DI P>Biodesign International
DI 105 York Street
DI Kennebunkport, ME 04043 USA
DI 1-207-985-1944
DI 2.P>Harlan Bioproducts for Science, Inc.
DI P.O. Box 29176
DI Indianapolis, IN 46229-0176
DI 1-317-894-7536
DI 1-800-9-SCIENCE
DE C>AMF7 ;developer
DE P>AMF7 ;distributor
DE P>P42770M ;distributor
DE 2.P>MCA 683 ;distributor
DO G>Mus musculus CN>mouse
PD ;IgG1
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51
RE 1.a.CC>differentiation
AV ;purified ;2.purified
SD AMF7
SD MCA683
SD P42770M
LD USA BAL
EI DA>9103 CV>9104
CT ;catalog
```

Your query was:
cd51

1021411 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet

```
1021411 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD51

AN 1021411
DI P>Immunotech S.A.
DI Departement commercial
DI Luminy Case 915
DI 13288 Marseille Cedex 9, France
DI 33-91-41-41-38
DI 430246 F IMMTECH
DE C>69-6-5 ;distributor
DE P>1603 ;distributor
DO G>Mus musculus CN>mouse S>BALB/c O>spleen
PD ;IgG2a
RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD51
RE 1.a.CC>protein
AV ;purified
SD 1603
SD 6965
LD USA JMJ
EI DA>9707
CT ;catalog
```

Your query was:
cd51

1015384 RE 1.G>Mus musculus 1.CN>mouse 1.SN>CD51

1015384 RE 1.G>Mus musculus 1.CN>mouse 1.SN>CD51

AN 1015384
DI P>PharMingen
DI 10975 Torreyana Road
DI San Diego, CA 92121 USA
DI 1-619-677-7737
DI 1-800-848-6227 (toll free USA)
DE C>H9.2B8 ;developer
DE P>01520D ;distributor
DE P>01521D ;distributor
DE P>01522D ;distributor
DE P>01524D ;distributor
DE P>01525B ;distributor
DO G>Cricetulus sp. CN>hamster
IF G>Mus musculus CN>mouse
PD ;IgG
RE 1.G>Mus musculus 1.CN>mouse 1.SN>CD51
RE 1.a.CC>differentiation
AP ;flow cytometry ;immunofluorescence
AV ;biotin conjugate ;fluorescein conjugate
AV ;phycoerythrin conjugate ;purified
SD 01520D
SD 01521D
SD 01522D
SD 01524D
SD 01525B
SD H92B8
LO USA BAL
EI DA>9408
CI ;catalog

This page was generated by SFgate 5.111.

Your query was:
cd51

1023962 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

```
1023962 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

AN 1023962
SO Cell 1992;69:11-25
DI P>Ancell Corporation
DI 243 Third Street North
DI P.O. Box 87
DI Bayport, MN 55003 USA
DT 1-800-374-9523 (toll free USA)
DI 1-612-439-0835
DE C>P2W7 ;distributor
DE P>202-020 ;distributor
DE P>202-030 ;distributor
DE P>202-040 ;distributor
DE P>202-050 ;distributor
TM G>Homo sapiens CN>human O>eye PA>melanoma CD>V+B2 a.CC>neoplasm
DO G>Mus musculus CN>mouse
PD ;IgG1 ;kappa
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51
RE 1.a.CC>differentiation
AP ;immunoprecipitation ;flow cytometry ;frozen section
AV ;R-phycoerythrin conjugate ;biotin conjugate
AV ;fluorescein conjugate ;purified
SD 202020
SD 202030
SD 202040
SD 202050
SD P2W7
LD USA MCM
EI DA>9608
CI ;catalog
```

This page was generated by SFgate 5.111.

Your query was:
cd51

1023559 RE 1.G>Mus musculus 1.CN>mouse 1.SN>integrin

1023559 RE 1.G>Mus musculus 1.CN>mouse 1.SN>integrin alpha V

SO Biochemistry 1990;29:10191
SO Exp Cell Res 1993;205:25
DI P>Upstate Biotechnology, Inc.
DI 199 Saranac Avenue
DI Lake Placid, NY 12946 USA
DI 1-617-890-8845
DI 1-800-233-3991 (toll free USA) (sales)
DE P>05-437 ;distributor
DO G>Mus musculus CN>mouse
RE 1.G>Mus musculus 1.CN>mouse 1.SN>integrin alpha V
RE 1.MW>160 kD 1.a.CC>differentiation 1.b.CC>receptor
AP ;Western blot ;immunoprecipitation ;immunohistochemistry
AV ;ascites
AB Reactant is also known as vitronectin receptor alpha subunit and CD51.
SD 05437
LD USA MCM
EI DA>9807
CI ;catalog

Your query was:
cd51

1023927 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin

1023927 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V

AN 1023927
SO J Biol Chem 1994;269:6940
DI P>Chemicon International, Inc.
DI 28835 Single Oak Dr.
DI Temecula, CA 92590 USA
DI 1-909-676-8080
DI 1-800-437-7500(toll free USA)
DE C>P3G8 ;distributor
DE P>MAB1953 ;distributor
IM G>Homo sapiens CN>human O>lung PA>carcinoma a.CC>neoplasm
DO G>Mus musculus CN>mouse
PD ;IgG1
RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
RE 1.a.CC>differentiation 1.b.CC>receptor
AP ;immunocytology ;immunohistochemistry ;immunoprecipitation
AP ;flow cytometry ;ELISA ;FACS
AV ;purified
AB Reactant is also known as CD51 and vitronectin receptor alpha subunit.
AB Product reacts with all alpha V-containing integrin receptors.
AB Product will react with some lymphoid cell lines (B cells), many carcinoma
AB melanoma cell lines and osteosarcomas.
SD MAB1953
SD P3G8
LD USA MCM
EI DA>9808
CI ;catalog

1015432 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51 1.FS

1015432 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51 1.FS>alpha subunit

AN 1015432
DI P>Biodesign International
DI 105 York Street
DI Kennebunkport, ME 04043 USA
DI 1-207-985-1944
DI 2.P>Caltag Laboratories
DI 1849 Bayshore Blvd. #200
DI Burlingame, CA 94010
DI 1-650-652-0468
DI 1-800-874-4007
DI 3.P>Cymbus Bioscience Limited
DI 2 Venture Road
DI Chilworth Research Center
DI Southampton, Hampshire SO1 7NS UK
DI 44-703-767178
DI 4.P>Endogen Inc.
DI 30 Commerce Way
DI Woburn, MA 01801-1059 USA
DI 1-781-937-0890
DI 5.P>Genosys Biotechnologies, Inc.
DI 1442 Lake Front Circle, Suite 185
DI The Woodlands, TX 77380-3600 USA
DI 1-713-363-3693
DI 1-800-234-5362 (toll free USA)
DI 6.P>Harlan Bioproducts for Science, Inc.
DI P.O. Box 29176
DI Indianapolis, IN 46229-0176
DI 1-317-894-7536
DI 1-800-9-SCIENCE
DI 7.P>Lampire Biological Laboratories
DI P.O. Box 270
DI Pipersville, PA 18947 USA
DI 1-215-795-2838
DI 8.P>PharMingen
DI 10975 Torreyana Road
DI San Diego, CA 92121 USA
DI 1-619-677-7737
DI 1-800-848-6227 (toll free USA)
DI 9.P>T Cell Diagnostics, Inc.
DI 6 Gill Street
DI Woburn, MA 01801-1721 USA
DI 1-800-624-4021
DI 1-617-937-9587
DE C>23C6 ;developer
DE P>23C6 ;distributor
DE P>P54490M ;distributor
DE 2.P>23C6 ;distributor
DE 2.P>MCN1167 ;distributor
DE 3.P>23C6 ;distributor
DE 3.P>CBL490 ;distributor
DE 4.P>23C6 ;distributor
DE 4.P>MA-5100 ;distributor
DE 5.P>23C6 ;distributor
DE 5.P>AM-19-760 ;distributor
DE 6.P>23C6 ;distributor
DE 6.P>MCA-757 ;discontinued designation
DE 6.P>MCA757G ;distributor

```
DE 7.P>23C6 ;distributor
DE 7.P>LBL 590 ;distributor
DE 8.P>23C6 ;distributor
DE 8.P>31561A ;distributor
DE 8.P>31564X ;distributor
DE 9.P>23C6 ;distributor
DE 9.P>IA1S04 ;distributor
DO G>Mus musculus CN>mouse
PD ;IgG1
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51 1.FS>alpha subunit
RE 1.MW>125 kD 1.a.CC>differentiation
AV ;purified ;4.purified ;6.purified ;8.fluorescein conjugate
AV ;8.purified ;9.supernatant
SD 23C6
SD 31561A
SD 31564X
SD AMI9760
SD CBL490
SD IA1S04
SD LBL590
SD MA5100
SD MCA757
SD MCA757G
SD MON1167
SD P54490M
LD USA BAL
EI DA>9706
CI ;catalog
```

Your query was:
cd51

1011348 RE 1.G>Homo sapiens 1.CN>human 1.SN>vitronect

1011348 RE 1.G>Homo sapiens 1.CN>human 1.SN>vitronectin receptor

AN 1011348
DI P>Chemicon International, Inc.
DI 28835 Single Oak Dr.
DI Temecula, CA 92590 USA
DI 1-909-676-8080
DI 1-800-437-7500(toll free USA)
DE P>CLB-706 ;distributor
DE P>MAB1980 ;distributor
RE 1.G>Homo sapiens 1.CN>human 1.SN>vitronectin receptor
RE 1.a.CC>receptor
AV ;purified
AB beta subunit of vitronectin receptor referred to as CD51 also
AB Reactant#1: vitronectin receptor beta subunit syn. for CD51
SD CLB706
SD MAB1980
LD USA BAL
EI DA>9107 CV>9108
CI ;catalog
SN Synonym>vitronectin receptor

CLAIMS:

1) A method of identifying a molecule which is an agonist of cell surface receptor CD36 and/or CD51 as expressed by mammalian dendritic cells which method comprises:

a) exposing immature mammalian dendritic cells to the molecule to be tested,

b) exposing said immature dendritic cells to an immune stimulus and

c) determining the degree of maturation manifested by said dendritic cells,

wherein impaired maturation in response to the immune stimulus is an indication that said molecule under test is a CD36 and/or CD51 agonist.

2) A method as claimed in claim 1 wherein said dendritic cells are human cells.

3) A method as claimed in claim 1 or 2 wherein maturation of said dendritic cells is determined by examining the antigen-presenting ability of said cells.

4) A method as claimed in any preceding claim wherein maturation of said dendritic cells is determined by examining said cells for expression of at least one cell surface antigen whose level of expression is enhanced in response to an immune stimulus.

5) A method as claimed in claim 4 wherein maturation of said dendritic cells is determined by measuring the level of expression of one or more of the following panel of antigens:
HLA DR, CD54, CD40, CD83 and CD86.

6) A method as claimed in claim 5 wherein said cells are also examined for expression of CD80.

7) A method as claimed in any one of claims 4 to 6 wherein the level of expression of said antigens is detected using a labelled antibody.

8) A method as claimed in 1 or 2 wherein maturation of said dendritic cells is determined by measuring said cells' ability to induce T-cell proliferation.

9) A method as claimed in any one of the preceding claims wherein said immune stimulus is lipopolysaccharide, TNFα, CD40L or monocyte conditioned medium (MCM).

10) A method as claimed in any preceding claim wherein if said test molecule is found to be a potential agonist of CD36 and/or CD51 the method further comprises the step of exposing said molecule to a purified sample of CD36 and/or CD51 and detecting any direct binding between said molecule and CD36 and/or CD51.

11) A method as claimed in claim 10 wherein said purified CD36 or CD51 is immobilised to a solid surface.

12) A method as claimed in claim 10 or claim 11

wherein said molecule is labelled with a detectable label.

13) A method as claimed in any of claims 10 to 12 which further comprises the step of exposing said molecule to a purified sample of $\alpha_v\beta_3$ or $\alpha_v\beta_5$ and detecting any direct binding between said molecule and said $\alpha_v\beta_3$ or $\alpha_v\beta_5$.

14) A method as claimed in any one of claims 10 to 13 which further comprises the step of exposing said molecule to a purified sample of thrombospondin and detecting any direct binding between said molecule and thrombospondin.

15) A method as claimed in claim 13 or claim 14 wherein said molecule is labelled with a detectable label.

16) A method as claimed in any of claims 13 to 15 wherein said $\alpha_v\beta_3$, $\alpha_v\beta_5$ or thrombospondin is immobilised to a solid surface.

17) A pharmaceutical composition suitable for inducing peripheral immune tolerance in a mammal which comprises an agonist of the cell surface receptor CD36 as expressed on mammalian dendritic cells and a pharmacologically acceptable carrier or diluent.

18) A composition as claimed in claim 17 which is suitable for inducing peripheral immune tolerance in a human wherein said CD36 agonist is selected from: an antibody with an affinity for an epitope of CD36, the Plasmodium falciparum protein pf-EMP-1,a protein comprising the active binding domain of pf-EMP-1 and

thrombospondin.

19) A composition as claimed in claim 18 wherein said CD36 agonist any one of the antibodies listed in Appendix 1.

20) A composition as claimed in claim 18 wherein the pf-EMP-1 active binding domain comprises the amino acid sequence as shown in Figure 2.

21) A composition as claimed in claim 16 wherein said CD36 agonist is a molecule identified as such by any one of the methods of claims 1 to 16.

22) An agonist of the cell surface receptor CD36 as expressed on mammalian dendritic cells for use as a medicament.

23) An agonist for use as claimed in claim 22 which is suitable for treating a human and wherein said CD36 agonist is selected from: an antibody with an affinity for an epitope of CD36, the Plasmodium falciparum protein pf-EMP-1, a protein comprising the active binding domain of pf-EMP-1 and thrombospondin.

24) An agonist for use as claimed in claim 23 wherein said CD36 agonist is any one of the antibodies listed in Appendix 1.

25) An agonist for use as claimed in claim 23 wherein the pf-EMP-1 active binding domain comprises the amino acid sequence as shown in Figure 2.

26) A pharmaceutical composition suitable for inducing peripheral immune tolerance in a mammal which

comprises an agonist of the cell surface receptor CD51 as expressed by mammalian dendritic cells and a pharmacologically acceptable carrier or diluent.

27) A composition as claimed in claim 26 suitable for inducing immune tolerance in a human wherein said CD51 agonist is selected from: an antibody with an affinity for an epitope of CD51 or thrombospondin.

28) A composition as claimed in claim 27 wherein said CD51 agonist is any one of the antibodies listed in Appendix 2.

29) A composition as claimed in claim 26 or 27 which comprises the Plasmodium falciparum protein pf-EMP-1 or a protein comprising an active binding domain thereof and thrombospondin.

30) A composition as claimed in claim 29 wherein said active binding domain of pf-EMP-1 comprises the amino acid sequence shown in Figure 2.

31) A composition as claimed in claim 26 wherein said CD51 agonist is a molecule identified as such by any one of the methods of claims 1 to 16.

32) An agonist of the cell surface receptor CD51 as expressed on mammalian dendritic cells for use as a medicament.

33) An agonist for use as claimed in claim 32 which is suitable for administration to a human wherein said CD 51 agonist is selected from: an antibody with an affinity for an epitope of CD51 or thrombospondin.

34) An agonist for use as claimed in claim 32 wherein said CD51 agonist is any one of the antibodies listed in Appendix 2.

35) An agonist for use as claimed in claim 31 which is suitable for administrration to a human and which comprises, in combination, the Plasmodium falciparum protein pf-EMP-1 or a protein comprising an active binding domain thereof and thrombospondin.

36) A method of treating mammalian dendritic cells in vitro to induce immune tolerance therein which comprises exposing said cells to an agonist of the cell surface receptors CD36 and/or CD51 as expressed on mammalian dendritic cells.

37) A method as claimed in claim 36 wherein said agonist is a molecule identified as such by any one of the methods of claims 1 to 16.

38) A method as claimed in claim 36 wherein said agonist is selected from: an antibody with an affinity for an epitope of CD36, an antibody with an affinity for an epitope of CD51, the Plasmodium falciparum protein pf-EMP-1, a protein comprising the active binding domain of pf-EMP-1 and thrombospondin.

39) A method as claimed in claim 36 which comprises exposing said dendritic cells to two or more of the agonists of claim 38.

40) A method as claimed in claim 38 or claim 39 wherein the CD36 agonist any one of the antibodies listed in Appendix 1.

41) A method as claimed in claim 38 or claim 39 wherein the CD51 agonist is any one of the antibodies listed in Appendix 2.

42) A method as claimed in claim 38 or claim 39 wherein the pf-EMP-1 active binding domain comprises the amino acid sequence shown in Figure 2.

43) A dendritic cell preparation produced by the method of any of claims 36 to 42 for use as a medicament.

44) A dendritic cell preparation produced by the method of any of claims 36 to 42 for use in inducing peripheral immune tolerance in a human.

45) Use of a method comprising the following steps for identifying a molecule capable of preventing the adherence of red blood cells infected with a malarial parasite to human dendritic cells:

a) exposing a purified preparation of the human cell surface receptor CD36 to:-

i) the molecule to be tested and
ii) parasitised human red blood cells,

either consecutively or simultaneously and

b) determining the level of adherence of said parasitised red blood cells to CD36

wherein a reduction in the level of adherence in the presence of the test molecule compared to the level in the absence of said molecule is an indication that

said molecule is capable of preventing the adherence of red blood cells infected with the malarial parasite to human dendritic cells.

46) Use of a method comprising the following steps for identifying a molecule capable of preventing the adherence of red blood cells infected with the malarial parasite to human dendritic cells:

a) exposing a purified preparation of human thrombospondin to:

i) the molecule to be tested and
ii) parasitised human red blood cells,

either consecutively or simultaneously and

b) determining the level of adherence of said parasitised red blood cells to thrombospondin,

wherein a reduction in the level of adherence to thrombospondin in the presence of the test molecule compared to the level in the absence of said molecule is an indication that said molecule is capable of preventing the adherence of red blood cells infected with the malarial parasite to human dendritic cells.

47) A method as claimed in claim 45 or claim 46 wherein said red blood cells are infected with Plasmodium falciparum.

48) A method as claimed in claim 47 wherein the Plasmodium falciparum strain is ITO/A4, ITO/C24 or MC.

49) A method as claimed in claim 45 wherein said CD36

is immobilised on a solid surface.

50) A method as claimed in claim 46 wherein said thrombospondin is immobilised on a solid surface.

51) A method as claimed in claim 49 or claim 50 wherein the level of adherence of said parasitised red blood cells to CD36 or thrombospondin is determined by the additional steps of:

a) washing the immobilised CD36 or thrombospondin to remove non-adhered red blood cells and

b) applying a stain to said immobilised CD36 or thrombospondin which is specific for parasitised or non-parasitised red blood cells.

52) A method as claimed in claim 51 wherein said stain is detectable by eye, by microscopy or by a spectrophotometric method.

53) A method as claimed in claim 45 which comprises applying simultaneously or consecutively the method of claim 46.

54) A method of identifying a molecule capable of preventing the adherence of red blood cells infected with a malarial parasite to human dendritic cells which comprises:

a) exposing immature human dendritic cells to the Plasmodium falciparum protein pf-EMP-1 or an active binding domain thereof in the presence or absence of the molecule to be tested,

b) exposing said immature dendritic cells to an immune stimulus and

c) determining the degree of maturation manifested by said dendritic cells,

wherein any maturation of said dendritic cells in the presence of the test molecule over and above that manifested in the absence of said molecule is an indication that said molecule is capable of preventing adherence of red blood cells infected with a malarial parasite to human dendritic cells.

55) A method as claimed in claim 54 wherein maturation of said dendritic cells is determined by examining the antigen-presenting ability of said cells.

56) A method as claimed in claim 54 or claim 55 wherein maturation of said dendritic cells is determined by examining said cells for expression of at least one cell surface antigen whose expression level is enhanced in response to an immune stimulus.

57) A method as claimed in claim 56 wherein maturation of said dendritic cells is determined by measuring the level of expression of two or more of the following panel of antigens:
HLA DR, CD54, CD40, CD83 and CD86.

58) A method as claimed in claim 56 wherein said cells are also examined for expression of CD80.

59) A method as claimed in any one of claims 56 to 58 wherein the level of expression of said antigen is detected using a labelled antibody.

60) A method as claimed in claim 54 wherein maturation is determined by measuring said cells' ability to induce T-cell proliferation.

61) A method as claimed in any one of claims 54 to 60 wherein said immune stimulus is lipopolysaccharide, TNF alpha, CD40L or monocyte conditioned medium (MCM).

62) A pharmaceutical composition useful for the treatment of malaria which comprises a molecule capable of preventing the adherence of red blood cells infected with the malarial parasite to human dendritic cells which has been identified by the method of any one of claims 54 to 61 and a pharmacologically acceptable carrier or diluent.

63) A molecule identified as being capable of preventing the adherence of red blood cells infected with the malarial parasite to human dendritic cells by the method of any one of claims 54 to 61 for use in the treatment of malaria.

64) A pharmaceutical composition useful for the treatment of malaria which comprises a molecule capable of preventing the adherence of red blood cells infected with the malarial parasite to human dendritic cells which has been identified by the use of the method of any one of claims 45 to 53.

65) A molecule identified as being capable of preventing the adherence of red blood cells infected with the malarial parasite to human dendritic cells by use of the method as claimed in any one of claims 45 to 53.

66) A method of identifying a molecule which is an agonist of cell surface receptors CD36 and/or CD51 as expressed on antigen-presenting cells of the mammalian immune system which method comprises:

a) exposing immature mammalian antigen-presenting cells to the molecule to be tested,

b) exposing said immature cells to an immune stimulus and

c) determining the response to said immune stimulus by said cells,

wherein an impaired response compared to the response in the absence of said test molecule is an indication that said molecule under test is a CD36 and/or CD51 agonist.

67) A method as claimed in claim 66 wherein said response is maturation of said antigen-presenting cell.

68) A method as claimed in claim 66 or 67 wherein said antigen-presenting cell of the immune system is selected from a dendritic cell, a macrophage, a B-lymphocyte or a monocyte.

69) A method as claimed in any of claims 66 to 68 which includes the features of any of claims 2 to 16.

70) A method of identifying a molecule which is an agonist a β-integrin associated with the cell surface receptor CD51 as expressed on antigen-presenting cells of the mammalian immune system which method comprises:

a) exposing immature mammalian antigen-presenting cells to the molecule to be tested,

b) exposing said immature cells to an immune stimulus and

c) determining the response to said immune stimulus by said cells,

wherein an impaired response compared to the response in the absence of said test molecule is an indication that said molecule is an agonist of a β-integrin associated with the cell surface receptor CD51.

71) A method as claimed in claim 70 which includes the features of any of claims 67 to 69.

72) A method as claimed in claim 70 or claim 71 wherein said β-integrin is β3 or β5.

72) A pharmaceutical composition suitable for inducing peripheral immune tolerance in a mammal which comprises an agonist of a β-integrin associated with the cell surface receptor CD51 as expressed on mammalian antigen-presenting cells and a pharmacologically acceptable carrier or diluent.

73) A pharmaceutical composition as claimed in claim 72 wherein the β-integrin is β3 or β5.

74) A method of inducing a state of immune tolerance in antigen-presenting cells of the mammalian immune system which comprises exposing said cells to an agonist of one or more of the cell surface receptors CD36, CD51 or a β-integrin associated with CD51.

75) A method as claimed in claim 74 wherein said β-integrin is β3 or β5.

FIG. 1.

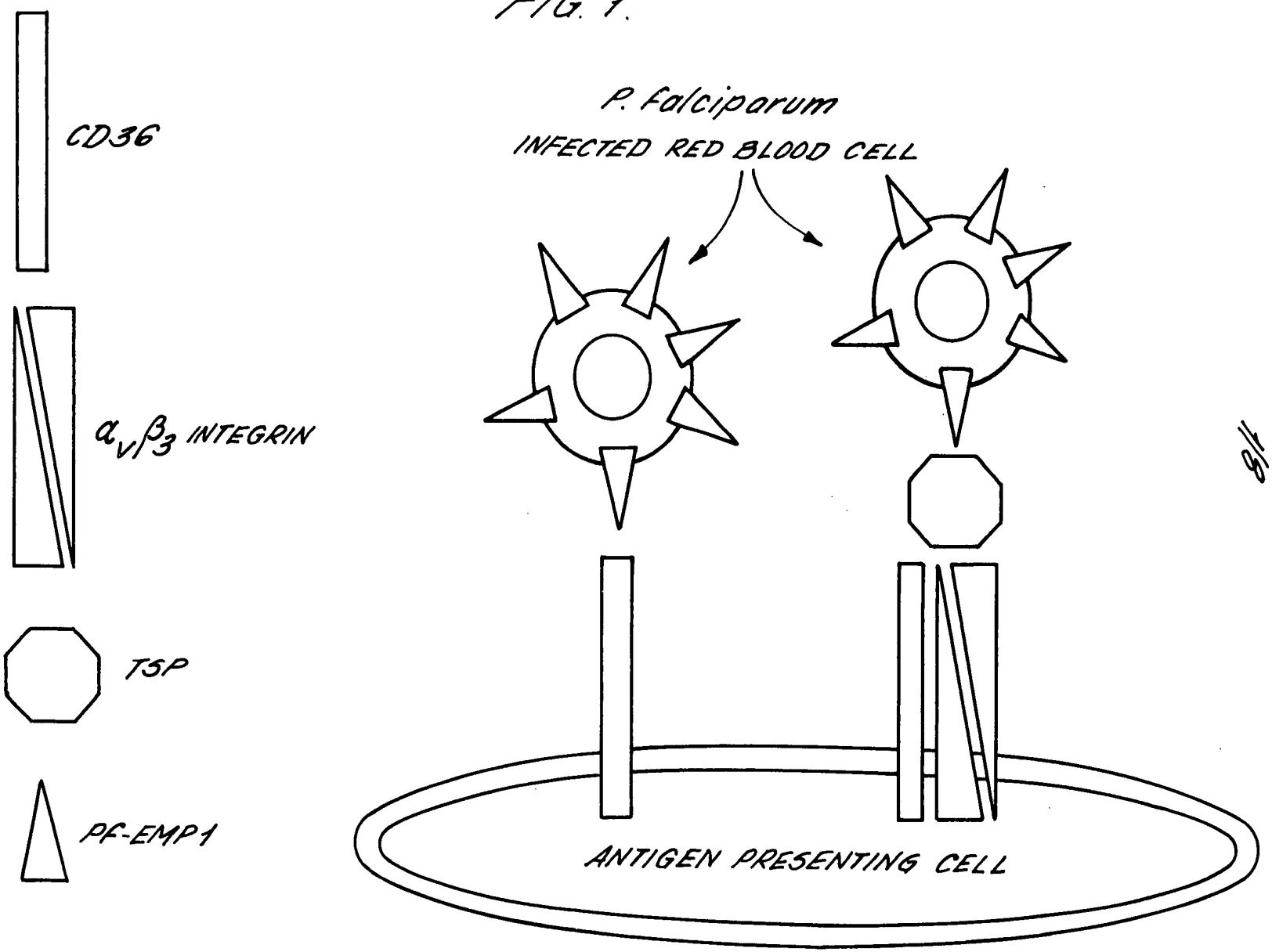

CD36
$\alpha_v\beta_3$ INTEGRIN
TSP
PF-EMP1
P. falciparum
INFECTED RED BLOOD CELL
ANTIGEN PRESENTING CELL

FIG. 2.

AMINO ACID SEQUENCE OF THE CIDR FRAGMENT OF THE A4-VAR GENE (COMPLETE SEQUENCE ACCESSION NO L42244)

402- TDEIKKNDD TTITTEYGTI NNMYRKDFYK HLEEKYKTVD

AFLNLLNKEK ECKNHPEVGE GKKKYIDFND NIETFSHTEY

REPCPWCGIE EQKDGKWKRI NDHSACKEEE LYTPKENAKY

TKINVLTSGE GHEDIAKRLK EFCTKTQNGG GGSDDCGGNS

DSSLCEPWQC YQPDQLEKVG GGEVDDKLKG AGGLCIFEKM

KGEKKVKKQK TFNNFFNFWV AHVLKDSIDW RTQLTKCLSE

DKLKKCEKGC KSNCECFKKW IEKKEKEWIK VKDQFNKQTD

FLEWKHYLVL ETILENYYFE NIQKAYGDLK SIQEMKKMIK

ENKQNKNRTK DDEDALDVLF DHEKEEAEDC LDIHEDDDDD

DECVEEIEKI PNNPCSGTRH RAMVKNVAAD MYRAARQQLR

NRAGGRKTLR ADASQGHYNG KANESVLKDV CDITNQYSNA

IGDSKD -846

FIG. 3.

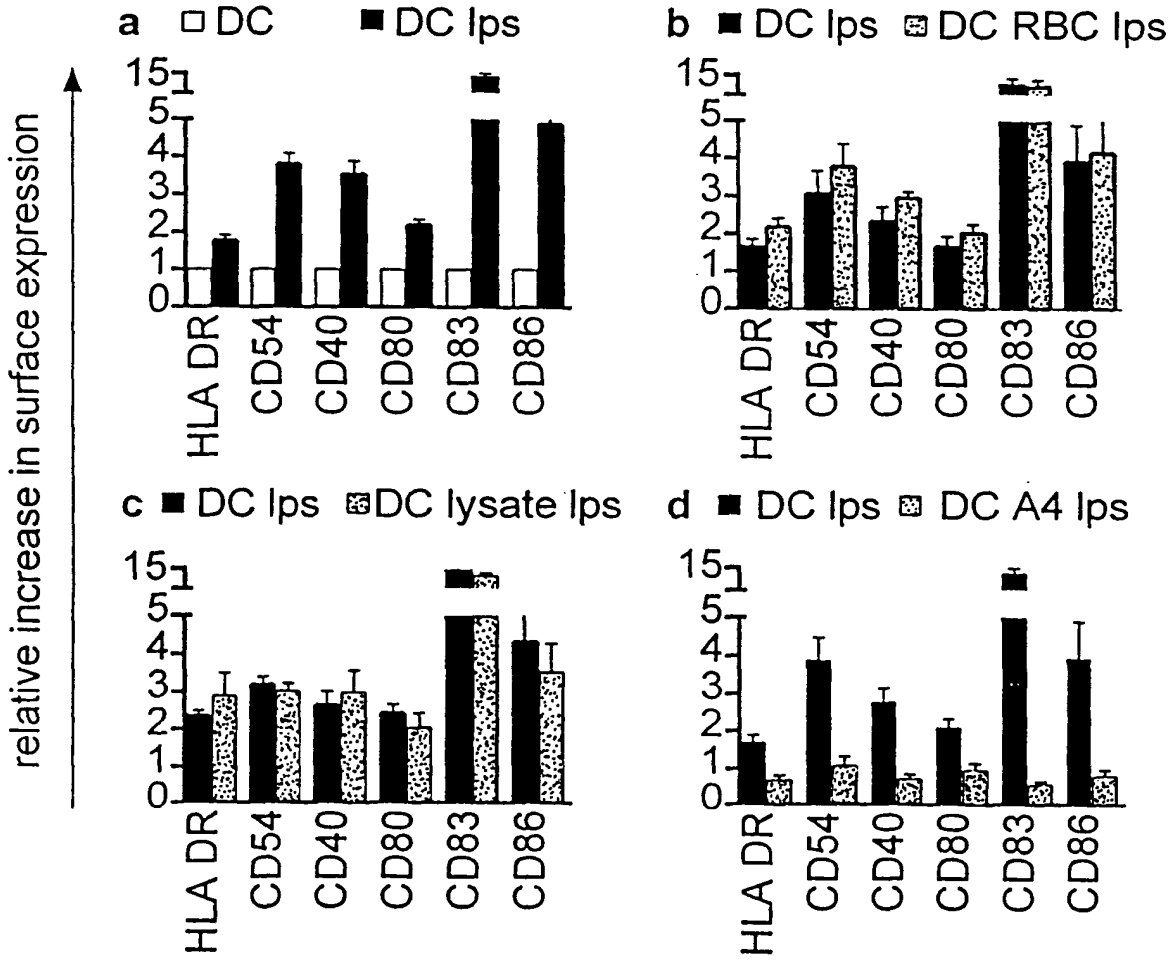
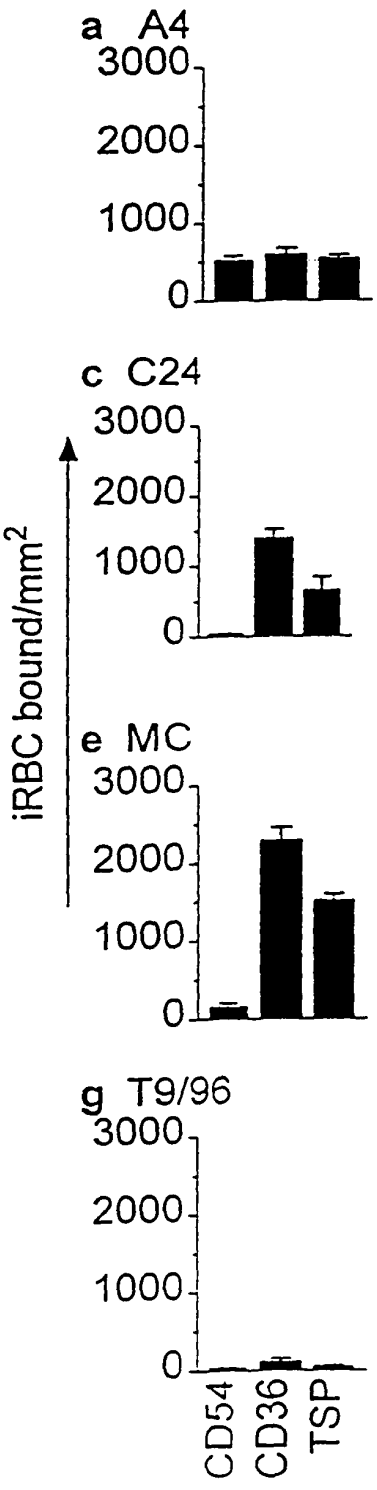

a DC DC Ips
b DC Ips DC RBC Ips
c DC Ips DC lysate Ips
d DC Ips DC A4 Ips
relative increase in surface expression
0
1
2
3
4
5
15
HLA DR
CD54
CD40
CD80
CD83
CD86

FIG. 4.

A.


a A4
3000
2000
1000
0
c C24
3000
2000
1000
0
e MC
3000
2000
1000
0
g T9/96
3000
2000
1000
0
CD54
CD36
TSP
iRBC bound/mm2

B.

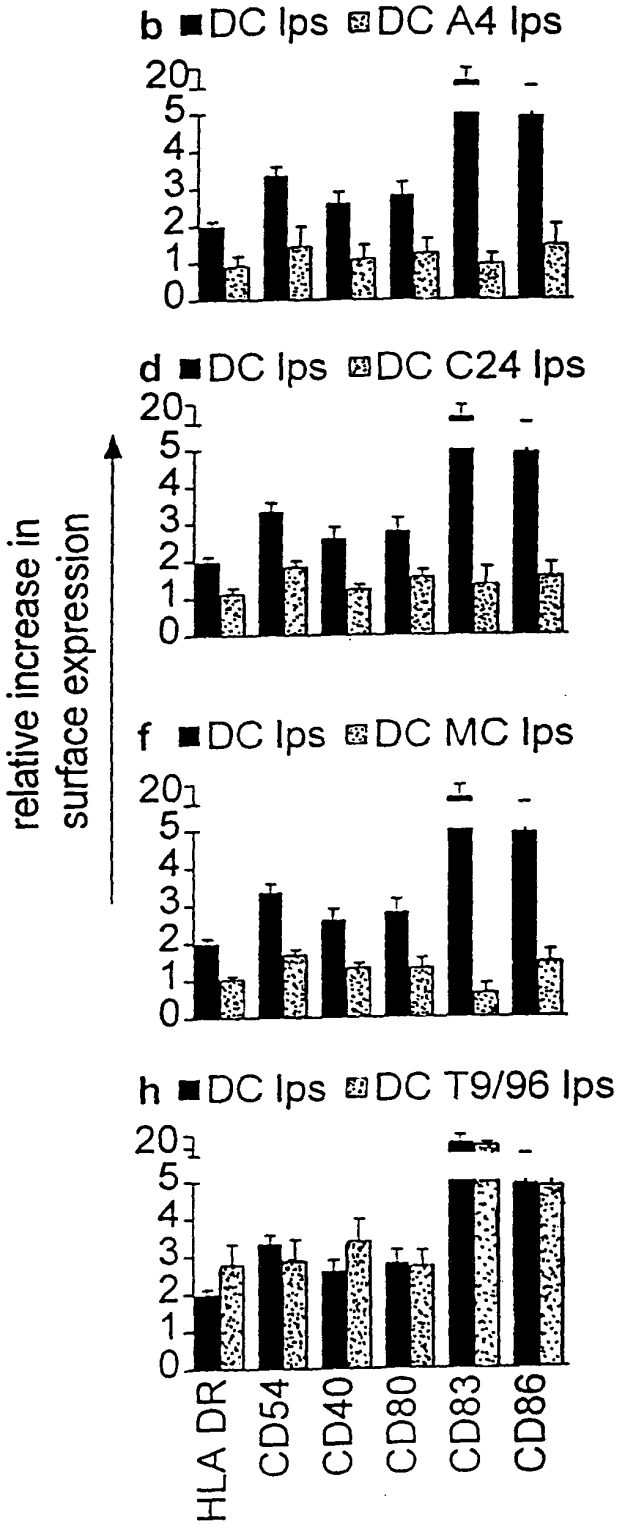

b DC Ips DC A4 Ips
d DC Ips DC C24 Ips
f DC Ips DC MC Ips
h DC Ips DC T9/96 Ips
20
5
4
3
2
1
0
HLA DR
CD54
CD40
CD80
CD83
CD86
relative increase in surface expression

FIG. 5.

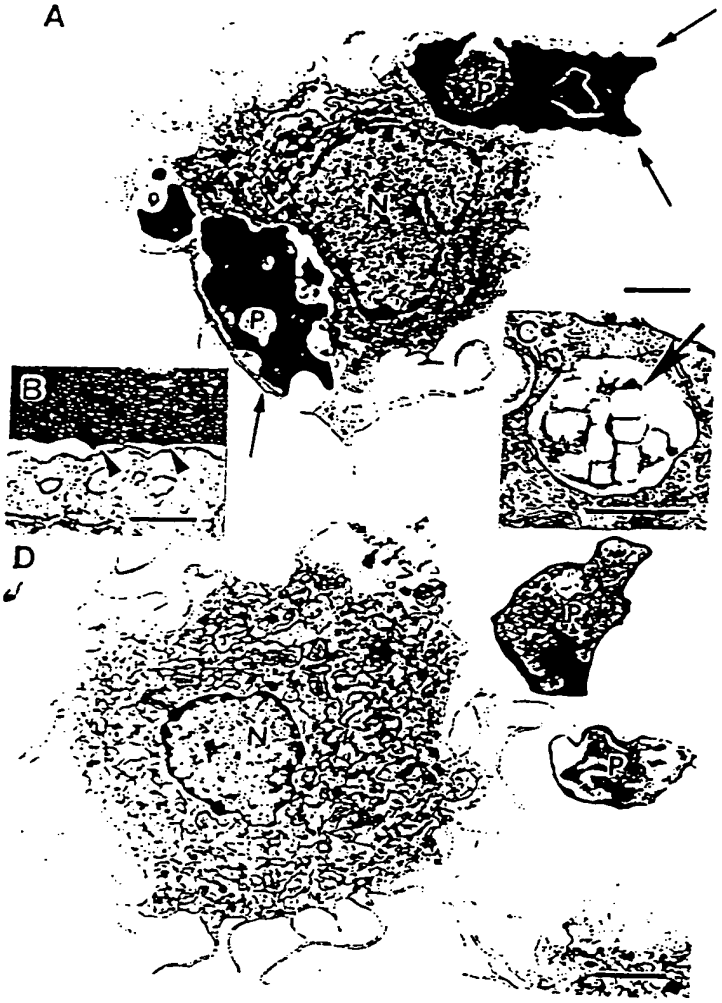


FIG. 6.

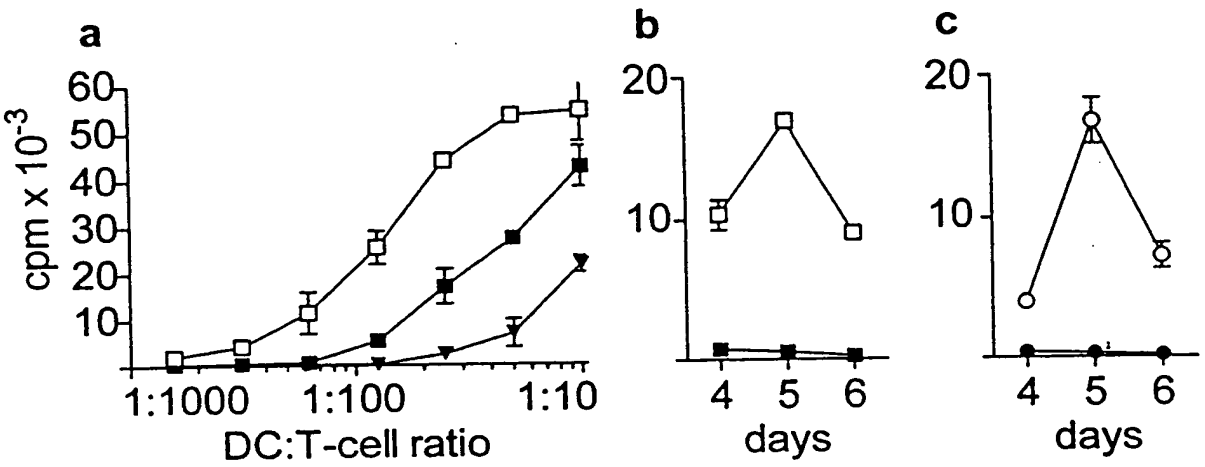
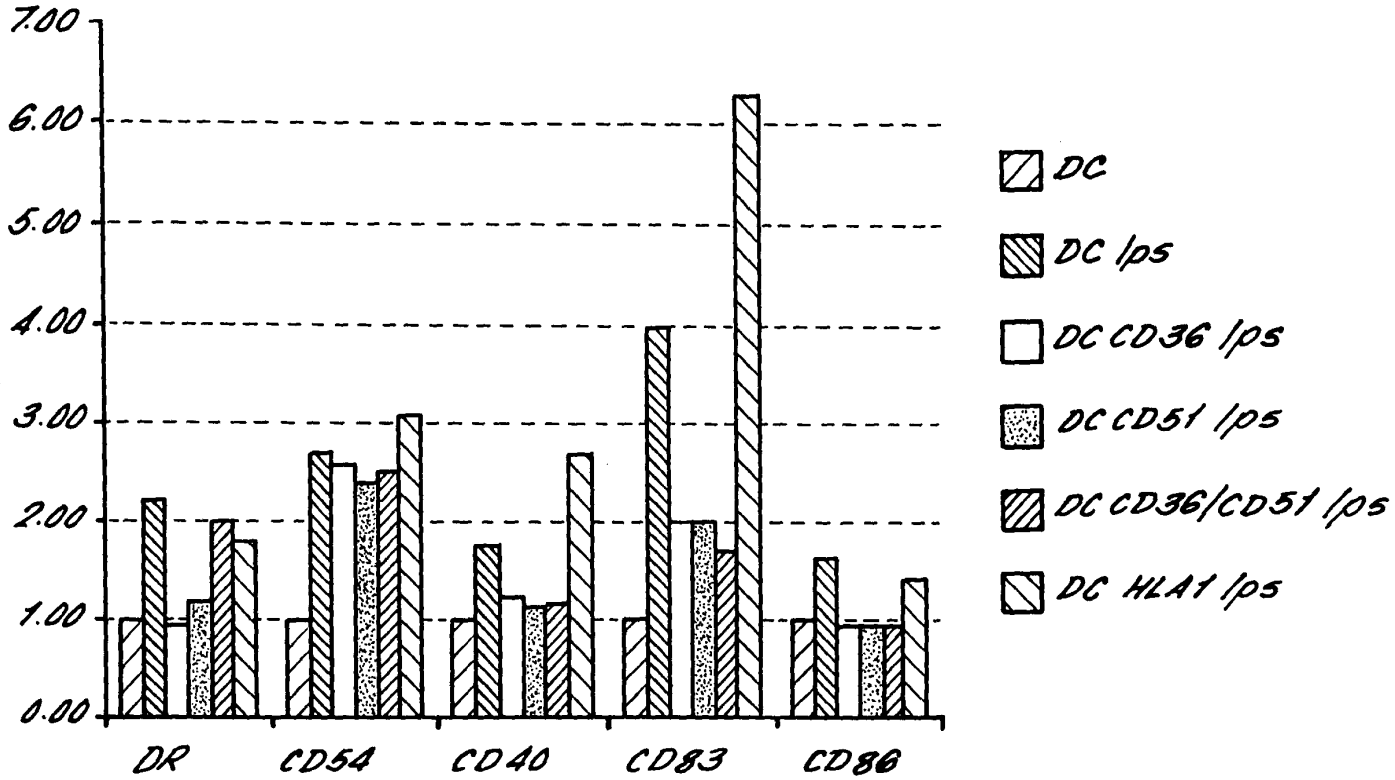

a
b
c
60
50
40
30
20
10
cpm x 10-3
1:1000
1:100
1:10
DC:T-cell ratio
20
10
4
5
6
days
20
10
4
5
6
days

FIG. 7


7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
DR
CD54
CD40
CD83
CD86
DC
DC lps
DC CD36 lps
DC CD51 lps
DC CD36/CD51 lps
DC HLA1 lps

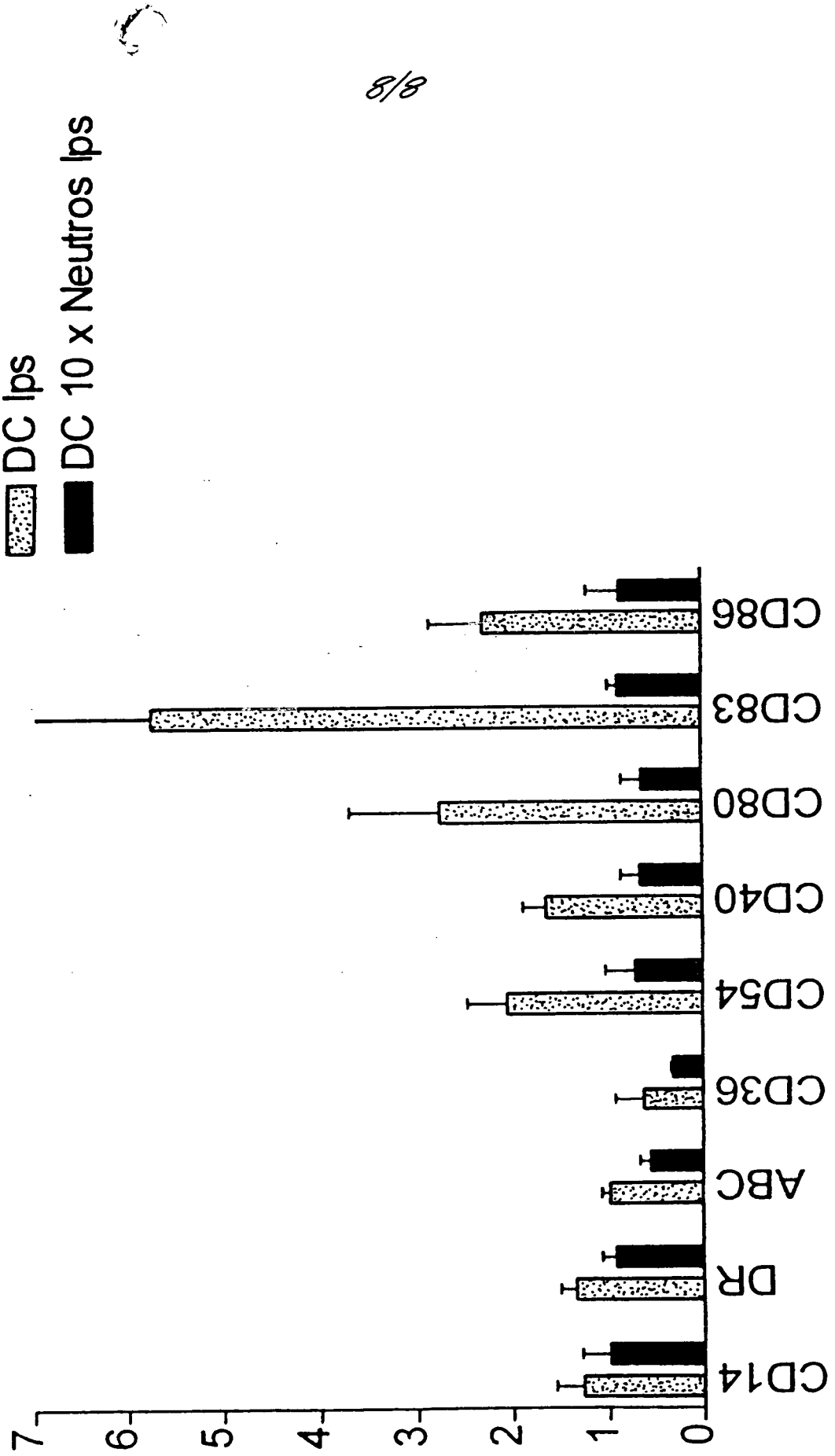

DC lps
DC 10 x Neutros lps
CD14
DR
ABC
CD36
CD54
CD40
CD80
CD83
CD86
0
1
2
3
4
5
6
7

FIG. 8.